Review Article

Indian J Med Res 147, March 2018, pp 239-247
DOI: 10.4103/ijmr.IJMR_1816_16

Quick Response Code:

Genotypes of erythrovirus B19, their geographical distribution & circulation in cases with various clinical manifestations

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Received November 9, 2016

Erythrovirus B19 (B19V) is one of the erythroviruses known to be pathogenic in humans. B19V is classified into three distinct genotypes; 1, 2 and 3, differing from each other by 2-13 per cent. Genotype 1 consists of the prototype B19V isolates, genotype 2 comprises the A6, LaLi and their related isolates while genotype 3 includes the V9- and V9-related isolates. The classification of genotype 1 into two subtypes (1A and 1B) and genotype 3 into two subtypes (3a and 3b) with an estimated nucleotide difference of about 5 per cent has been done. Predominance of genotype 1 across all the continents is seen followed by genotypes 2 and 3. There are no disease-specific genotypes. All the three genotypes have been found in symptomatic as well as asymptomatic individuals and have been reported from several countries across the world. The prevalence of genotype 2 in older populations and its absence from current circulation in Northern Europe has also been reported. The present review focuses on geographic distribution and association of genotypes of B19V with different clinical manifestations.

Key words B19V - B19V genotypes - erythroviruses - geographical distribution - parvovirus - parvovirus B19

Introduction

Erythrovirus B19 (B19V) is a rather recently discovered virus, which has been associated with a spectrum of diseases, including erythema infectiosum in children (fifth disease), acute or chronic arthropathy in adults, transient aplastic crisis in patients with chronic haemolytic anaemia, persistent anaemia in immunodeficient/immunocompromised patients, and foetal hydrops in pregnant women[1]. Many genotypes of B19V (genotypes 1-3) are circulating; however, a comprehensive review on their geographic distribution and their association with different clinical manifestation is lacking. Therefore, the present review was written with a focus on geographic distribution and association of genotypes of B19V with different clinical manifestations.

Members of the family *Parvoviridae* are among the smallest known DNA-containing viruses that infect mammalian cells (*Parvum* 'small'; Latin). The *Parvoviridae* family contains many viruses which are pathogenic to animals, and erythovirus B19 (B19V) is one of them. B19V is also one of the best-characterized members and is classified as a member of the *Erythroparvovirus* genus. Family *Parvoviridae* is divided into two subfamilies; *Parvovirinae* and *Densovirinae*. The *Parvovirinae* is further subdivided into eight genera, *Protoparvovirus* (previously known as *Parvovirus*), *Dependoparvovirus,*

Erythroparvovirus, Bocaparvovirus, Amdoparvovirus, Aveparvovirus, Copiparvovirus and *Tetraparvovirus*. At least four different parvoviruses are known to infect humans: Parvovirus B19, human adeno-associated viruses (dependoparvoviruses), human bocaparvovirus (HBoV) and human Parv4 virus (a member of the newly created *Tetraparvovirus* genera)[2].

B19V was discovered in 1975, in the serum samples of normal human individuals, during evaluation of assays for hepatitis B surface antigen using panels of serum samples[3]. Sample 19 in panel B (hence B19) gave a 'false positive' result in relatively insensitive counter immunoelectrophoresis assay. The precipitin line under electron microscopy showed 23 nm particles resembling parvoviruses[3]. Association of B19V infection with human diseases was first time made in 1981[4], and was subsequently identified in several experimental and seroepidemiologic studies[5,6]. B19V was identified as the causative agent of fifth disease (erythema infectiosum), common childhood exanthema and a polyarthralgia syndrome in adults[7,8]; transient aplastic crisis in patients with underlying haemolysis[4]; and spontaneous abortion[9]. Role of B19V in liver manifestations and hepatitis is also known[10].

Although originally labelled as human parvovirus, the virus was officially recognized as a member of the family *Parvoviridae* in 1985, and the International Committee on Taxonomy of Viruses recommended the name B19V to avoid confusion with other viruses[2]. Parvovirus forms small icosahedral capsids of about 25 nm. The genome size of B19V is small, consisting of a single strand of DNA of approximately 5600 nucleotides, with identical 365 nucleotide long inverted terminal repeat sequences at each end[11].

Genotypes of human erythrovirus

It was only about till three decades ago when researchers realized that genetic variations among parvoviruses exist. Since 2000, many B19V genotypic variants have been reported which vary extensively from the prototype B19V with respect to genomic sequence, exhibiting >13 per cent divergence versus the <2 per cent divergence in characteristic of previously characterized prototype B19V isolates[12-15].

In the first effort of genotyping parvoviruses, the genome of 17 strains of the human parvovirus B19V was compared after restriction with eight endonucleases. All but four strains proved indistinguishable[16]. Following this study, another study from Japan used DNA fingerprinting to demonstrate that the strains of parvoviruses circulating during 1981 were different from the strains circulating during 1986-1987[17]. Based on further studies and phylogenetic analysis, the B19V was classified into three distinct genotypes[12-14]. Genotype 1 consists of all the prototype B19V isolates, A6, LaLi and their related isolates are included in genotype 2[18-20], and genotype 3 is composed of V9 and V9-related isolates[20,21].

Further, phylogenetic analyses revealed two subgroups within both genotypes 1 and 3. The analysis of 13 nearly full-length genotype 3 sequences from Ghana, Europe and Brazil identified two genetically distinct clusters, following which the classification of genotype 3 into two subtypes (3a and 3b) was made[22]. Rate of evolutionary change in strains of B19V genotype 3 (2×10^{-4} nucleotide substitutions per site per year) was similar to that of other B19V genotypes. The estimated divergence time between 3a and 3b was 525 years. Subtype 3a was predominant in Ghana[22].

B19V genomes from Vietnam showed two major subgroups within genotype 1 (1A and 1B) with an estimated nucleotide difference of >5 per cent between each subgroup. The mean percentage of amino acid variation in NS1, VP1 and VP2 proteins, between both subgroups was >2 per cent[23].

Reported nucleotide and amino acid changes among various genotypes are summarized in Table I. The most striking variation was observed within the promoter area (~20%). Within the *NS1* gene, sequence divergence between genotypes 1, 2 and 3 was about 13 per cent at the nucleotide level. The two identical terminal repeats (ITRs) of approximately 365 nucleotides seen in B19V genotype 1 genome are imperfect palindromes and form hairpin loops. The terminal repeats of genotypes 2 and 3 have not been yet cloned and sequenced[15,24,25]. The sequence of a human erythrovirus, termed V9, was markedly distinct (>11% nucleotide divergence) from that of B19V[27]. One V9-related strain (D91.1) with 5.3 per cent divergence from V9 and 13.8-14.2 per cent divergence to prototype B19V sequences was reported[26]. A6, a new atypical parvovirus sequence, exhibited 88 per cent similarity to prototype B19V and 92 per cent similarity to V9, compared to >98 per cent similarity between earlier reported B19V strains[26]. K71, a new B19V genotype, is carried in human skin and differs from prototype B19V by 10.8 and 8.6 per cent within protein-coding regions and non-coding region (covering nucleotides 189-435 of the promoter region) respectively, while divergence from V9 variant was 26.5 and 17.2 per cent within protein-coding regions

Table I. Nucleotide and amino acid variance among different genotypes of B19V

B19V genotypes under study	B19V reference strain	Nucleotide/amino acid divergence	References
Genotype 1, 1A variant	1B variant	Nucleotide difference >5% Amino acid variation >2%	23
Genotype 2	Genotype 1	1.4% amino acid sequence in NS1	24,25
Genotype 2	Genotype 1	4.4% amino acid divergence within the VP1 unique region (uVP1), mainly at N termini	24,25
Genotype 2	Genotype 1	9% nucleotide level divergence in VP1/2 proteins	24,25
Genotype 2, A6 variant	Genotype 1	6.2% amino acid sequence in NS1	24,25
Genotype 2, A6 variant	B19V	12.0% nucleotide divergence	26
Genotype 2, A6 variant	V9 variant	8.0% nucleotide divergence	26
Genotype 2, K71 variant	B19V	10.8% nucleotide divergence in protein-coding regions 8.6% nucleotide divergence in non-coding region	12
Genotypes 2 and 3	Genotype 1	~20% nucleotide change in promoter area	24,25
Genotypes 2 and 3	Genotype 1	~13% divergence at the nucleotide level in *NS1* gene	24,25
Genotype 3	Genotype 1	6.2% amino acid sequence in NS1	24,25
Genotype 3	Genotype 1	12% nucleotide level divergence in VP1/2 proteins	24,25
Genotype 3	Genotype 1	6.6% amino acid divergence within the VP1 unique region (uVP1), mainly at N termini	24,25
Genotype 3, V9 variant	Genotype 1	1.1% amino acid sequence in NS1	24,25
Genotype 3, V9 variant	B19V	>11% nucleotide divergence	27
Genotype 3, D91.1 variant	V-9 variant	5.3% nucleotide divergence	13
Genotype 3, D91.1 variant	B19V	13.8-14.2% nucleotide divergence	13

and non-coding region (covering nucleotides 189-435 of the promoter region), respectively[12]. The amino acid sequence of A6 and V9 variants in NS1 protein diverges from that of the B19 V prototype-encoded counterpart by 6.2 and 6.1 per cent, respectively[24,25]. Within the open reading frame encoding the VP1/2 proteins, genotypes 2 and 3 differ from the prototype B19V by 9 and 12 per cent, respectively, at the nucleotide level. However, at the amino acid level the difference is much less, 1.1 and 1.4 per cent. Genotypes 2 and 3 differ from genotype 1 by 4.4 and 6.6 per cent, respectively in the VP1 unique region (uVP1). *uVP1* gene containing the reported phospholipase 2 activities (amino acids 130-195) is highly conserved, and variation is mostly seen in the N termini[24,25]. The capsid protein sequence is conserved between the different genotypes, in spite of differences in the DNA sequences, as there is enough evidence in serologic and cross-neutralization reactions[28-30].

Persistence of B19V in human tissues and distribution of B19V genotypes

Several studies have suggested that after primary infection, in both symptomatic and asymptomatic subjects[31-33] and in both immunocompromised and immunocompetent hosts[34] the erythroviral genomic DNA is detectable in tissues. The genotype 1 replicates restrictively in the erythroid progenitors of human bone marrow producing high viral load viraemia[11,29]. In contrast, high virus-load viraemia of genotypes 2 and 3 has been identified only occasionally[13,14,30,35]. Manning *et al*[34] discussed the persistence of B19 in human tissues in immunocompetent hosts. A study by Norja *et al*[36] done on a large number of human tissues including synovial, skin, tonsil and liver tissues and human serum samples concluded, "erythrovirus genome persistence in human tissues is ubiquitous and lifelong and represents an entity, named the *Bioportfolio*, which indicates that the newly discovered virus type 2 was actually 'older' in occurrence in Central and Northern Europe than the virus prototype and that the type 3 never attained wide circulation in the area during the 70 years observation period from the 1930s to the present day". However, in north India, genotype 3 has been detected in cases of cardiomyopathy[37] and solid tumors[38]. This analysis signifies that the distribution of genotypes is geographically restricted and distribution may change

with time. Manning *et al*[34] also maintained that B19V genotype 2 was more commonly seen in older study subjects, while B19V genotype 1 was commonly seen in younger subjects. Studies published from Germany, Italy and Finland, after 2007 demonstrated presence of all the three genotypes 1, 2 and 3, both in patients and asymptomatic controls. Genotype 2 was also demonstrated in blood and tissue biopsies[39-43]. One study from South Africa detected genotype 2 from serum of a child providing evidence for its circulation[44].

Only a single serotype of B19V is suggested as seen by 100 per cent cross-reactivity of antibodies among these three genotypes[45].

Geographical distribution of circulating genotypes in various countries

Many studies have reported genotypes of B19V in human infections. Table II summarizes the studies with genotypic details of B19V. Studies are available from Europe, Asia, South America and Africa. Very limited or no data are available from North America and Australia. Table III shows the number and frequencies of total strains which have been genotyped from each geographical area. Only those continents from where more than three studies were available, are included in analysis.

Europe

Genotype 1 was most frequently seen (61.64%), followed by genotype 2 (36.73%) and genotype 3 (1.62%) (Table III). In most of studies from Germany, done on cases of cardiomyopathy, either genotype 1 or genotype 2 was detected[39,40,43,44], with occasional reports of genotypes 3[47]. Studies done on transplant recipients[41], patients with hepatitis[46] and dilated cardiomyopathy[47] from Germany, showed presence of all the three genotypes, although genotype 1 was predominant. Predominantly genotypes 1 and 2[49,69] were reported from Italy with occasional reports of genotypes 3 from two asymptomatic individuals[48]. Of the six B19V positive transplant recipients, one was positive for active infection with genotype 1 and genotype 5 was either reactivation or re-infection of genotype 2[51] as reported from France. In a landmark study from France, where both prospective and retrospective samples collected during 1972-2001, were analyzed, mainly genotype 1 was detected. Genotype 3 was detected (~11%) in samples collected during 1999-2001[14]. In a single study from Poland, genotype 3 was not found[50]. Studies from the UK[34] and Finland[42] demonstrated only genotype 1. In a study from Bulgaria, genotype 2 was not demonstrated[52].

Asia

Studies are available from many countries including China, India, Russia, Korea, Vietnam and Iran; however, no large-scale studies on B19V genotypes are available. Based on the available data, genotype 1 is most commonly reported genotype (95.7%), while genotype 2 (1.4%) and genotype 3 (2.9%) have been occasionally reported (Table III). Studies done in Vietnam[53] reported that majority of strains were genotype 1 with occasional reports of genotype 2. Genotype 3 was not reported from any other countries in Asia, except India, from where only occasional reports are available; however, genotype 2 was never reported from India[58]. In studies done from Iran[59], China[55,56], Russia[57], Korea[60] and Thailand[54] only genotype 1 was reported. In north India genotype 3 was detected in cases of cardiomyopathy[37], and solid tumors[38].

South America

Only one study from Brazil, which was published on cases with haematological disorders, reported a single strain of genotype 2[20]. Based on available reports, genotypes 1 and 3 are present in frequencies of 87.94 and 11.70 per cent, respectively (Table III). Some of the studies showed prevalence of both genotype 1 (commonly) and genotype 3 (rarely)[61,65,66], while other studies showed the prevalence of genotype 1 only[62,64,67].

Africa

Genotype 1 has been most frequently reported (66.4%), followed by genotype 3 (22.1%) and genotype 2 (11.5%) (Table III). In a study done on pregnant women, predominantly genotype 3 was reported with occasional prevalence of genotype 1[67], while another study reported all the three genotypes[44]. Genotype 3 was not reported in studies from Gabon[51] and Nigeria[68].

North America

In a study from the USA[70] done on cases of cardiomyopathy genotype 3 was not detected. Majority of the strains were genotype 1 with occasional presence of genotype 2. In another study 204 strains from the USA were genotyped retrospectively and all of them were genotype 1[14].

Erythrovirus B19 genotypes and their associations with diseases

As shown in Table IV, prevalence of each genotype among various clinical groups varied significantly. Since genotype 1 was the most commonly reported

Table II. Prevalence of B19V genotypes as reported by different studies

Study population	Number of strains genotyped	Gene sequenced	Country	1	2	3	Year of publication	References
Europe								
Myocarditis	498	P6-promoter region	Germany	286	212	0	2005	28
Hepatitis patients liver specimens tested	59	*NS1/VP1* gene	Germany	32	23	4	2008	46
Dilated cardiomyopathy	151	*NS1/VP1* gene	Germany	43	108	0	2008	40
Cardiomyopathy	85	*VP1* gene	Germany	9	76	0	2009	39
Myocarditis	7	*VP1* gene	Germany	3	4	0	2009	43
Dilated cardiomyopathy	65	*VP1* gene	Germany	38	25	2	2011	47
Adult transplant recipients	15	*VP1/VP2* gene	Germany	12	2	1	2013	41
HIV positives	13	*NS1* gene	United Kingdom	13	0	0	2007	34
Asymptomatic individuals	55	*NS1/VP1* gene	Italy	19	34	2	2008	48
Systemic sclerosis (SSc)	29	*NS1/VP1* gene	Italy	18	11	0	2009	49
Symptomatic B19V infection	38	*NS1/VP1* gene	Poland	36	2	0	2011	50
Hematopoietic stem cell transplant recipients	16	*VP1* gene	Finland	16	0	0	2013	42
Suggestive B19V infection	192	NS1/VP1 restriction fragment	France	181	0	11	2002	14
Kidney transplant recipients	6	*VP1/VP2* gene	France	1	5	0	2013	51
Fever with rash	109	*NS1* gene	Bulgaria	106	0	3	2014	52
Asia								
Hepatitis B virus positive individuals	49	*NS1/VP1* gene	Vietnam	47	2	0	2013	53
Thalassaemia patients	8	*NS1* gene	Thailand	8	0	0	2007	54
Blood donors	23	*NS1/VP1* gene	China	23	0	0	2011	55
HIV positives	26	*NS1* gene	Siachun in China	26	0	0	2012	56
Maculopapular rash	8	NS1-VP1 gene junction	Russia	8	0	0	2013	57
Cardiomyopathy	2	*VP1* gene	India	0	0	2	2013	37
Children with haematological malignancies	13	*VP1/VP2* gene	India	11	0	2	2015	58
HIV positives and controls	21	*VP1* gene	Iran	21	0	0	2015	59
Plasmapheresis donors	10	*NS1/VP1* gene	Korea	10	0	0	2007	60

Contd...

Study population	Number of strains genotyped	Gene sequenced	Country	1	2	3	Year of publication	References
South America								
Haematological disorder	12	*NS1* gene	Brazil	5	1	6	2006	20
Wide spectrum of clinical presentations suggestive of erythrovirus infections	117	Partial VP1 and VP2	Brazil	106	0	11	2008	61
Erythema infectiosum, arthropathy, severe anaemia, transient aplastic crisis	97	NS1-VP1 gene junction	Brazil and Paraguay	97	0	0	2011	62
Sickle cell disease and thalassaemia	9	*NS1* gene	Brazil	9	0	0	2012	63
Sickle cell disease	2	*NS1*/*VP1* gene	Brazil	2	0	0	2013	64
Leukaemia	40	*NS1* and *VP1*/*VP2* gene	Brazil	25	0	15	2013	65
HIV positives	5	*VP1*/*VP1* gene	Brazil	4	0	1	2014	66
Africa								
Pregnant women	16	*VP1*/*VP2* gene	Ghana	1	0	15	2006	67
B19V infection suspect	53	*NS1* gene	South Africa	40	3	10	2010	44
Acute and chronic hepatitis	15	*VP1* gene	Nigeria, Africa	13	2		2011	68
Children with falciparum malaria and controls	29	*NS1*/*VP1* gene	Gabon, Africa	21	8	0	2013	53

Table III. Frequencies of human erythrovirus B19 genotypes in different continents

Continents	Genotypes (%)			Total strains genotyped and reported
	1	2	3	
Europe[14,28,34,39-43, 46-52]	871 (61.64)	519 (36.73)	23 (1.62)	1413
Asia[37,53-60]	133 (95.7)	2 (1.4)	4 (2.9)	139
Africa[44,53,67,68]	75 (66.4)	13 (11.5)	25 (22.1)	113
South America[20,61-66]	248 (87.94)	1 (0.354)	33 (11.70)	282
P	<0.001	<0.001	<0.001	

Chi-square (ψ) test. Numbers in superscript denote references

genotype, its predominance in most of the clinical situations was also noticed except in individuals with cardiac manifestations, where genotype 2 was predominantly reported (Table IV). The site of virus detection (various tissues or blood) varied from study to study. All the three genotypes have been detected in different proportions from cases presenting with different clinical manifestations, for example, anaemia, aplastic crisis, erythema infectiosum, arthropathy and cardiomyopathy. All the three genotypes have been found in symptomatic as well as normal individuals (Table IV).

Conclusion

B19V is classified into three distinct genotypes 1, 2 and 3, differing from each other by 2-13 per cent. The classification of genotype 3 strains into two subtypes (3a and 3b) and genotype 1 into two subtypes (1A and 1B) has been made. Predominance of genotype 1 across all the continents is seen followed

Table IV. Frequency of human erythrovirus B19 genotypes in various clinical conditions

Clinical conditions	Genotype (%)			Total
	1	2	3	
Cardiac manifestations	379 (46.90)	425 (52.59)	4 (0.495)	808
Co-infection with other pathogens	337 (86.85)	36 (9.27)	15 (3.86)	388
Haematological disorders/autoimmune diseases	131 (74.43)	28 (15.90)	17 (9.65)	176
Classical manifestation of B19V infection	398 (91.70)	6 (1.38)	30 (6.91)	434
Transplant recipients	29 (78.37)	7 (18.91)	1 (2.7)	37
Asymptomatic individuals	53 (50.96)	34 (32.69)	17 (16.34)	104

Source: Refs. 14, 20, 28, 34, 37, 39-44, 46-68

by genotypes 2 and 3. There are no disease-specific genotypes and association of genotypes with clinical manifestations has not yet been established. All the three genotypes have been found in symptomatic as well as asymptomatic individuals and have been reported from several countries across the world. The prevalence of genotype 2 in older populations and its absence from the current circulation in Northern Europe has been reported.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

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